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EDITORIAL

Kidney in primary aldosteronism: A key determinant of treatment outcome

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Abstract

Recently, it has been suggested that primary aldosteronism (PA) is associated with a variety of cardiac, vascular, metabolic, and renal sequelae that reflect the capability of elevated aldosterone to induce organ damage beyond that induced by hypertension itself. The evidence supporting of these views has been obtained from experiments conducted in rodents and clinical studies conducted in patients with this endocrine disorder. It has been suggested that untoward effects of high-salt intake are dependent on activation of mineralocorticoid receptors that might result from increased oxidative stress and changes in the intracellular redox potential. Unilateral adrenalectomy or treatment with mineralocorticoid receptor antagonists are the current options for treating an aldosterone-producing adrenal adenoma or idiopathic adrenal hyperplasia. Treatments are largely effective in correcting hypertension and hypokalemia, and currently available information on their capability to prevent deterioration of renal function indicates that surgery and medical treatment are equally beneficial in the long term. This editorial review will focus on the renal aspects of PA and highlights the role of the kidney as a key determinant of both adaptation to aldosterone-induced volume retention and response of blood pressure to treatment.

Key words: Blood pressure; Glomerular filtration rate; Albuminuria; Adrenalectomy; Mineralocorticoid receptor antagonists

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INTRODUCTION

Primary aldosteronism (PA), the most common form of curable hypertension, is characterized by low plasma potassium, metabolic alkalosis, suppressed plasma renin, and non suppressible aldosterone secretion resulting from either an adrenal adenoma (aldosterone-producing adenoma) or idiopathic adrenal hyperplasia. Recent evidence clearly indicates a greater frequency of PA among patients with high blood pressure than the previously ac-

cepted prevalence of approximately 1%[1-3]. This increase in apparent prevalence is the result of widespread use of the aldosterone-to-renin ratio as a screening test that has led to a more efficient identification of this disorder[4,5].

PA was traditionally considered a relatively benign form of hypertensive disease[6], a fact that was generally ascribed to suppression of renin activity and angiotensin II generation that are the consequence of the aldosterone-induced expansion of the extracellular fluid volume[7]. More recent authors have, however, suggested that exposure to excess aldosterone levels might result in substantial cardiovascular[8] and renal damage[9]. Our current knowledge indicates that PA is associated with a variety of cardiovascular and renal sequelae[10] reflecting the capability of aldosterone to induce tissue damage beyond that induced by hypertension itself.

Aldosterone-producing adenoma and bilateral idiopathic adrenal hyperplasia are the common causes of PA, and the currently treatments are adrenalectomy or mineralocorticoid receptor antagonists respectively. Both surgical and medical treatments effectively reduce blood pressure and normalize biochemical abnormalities that characterize PA. However, normalization of blood pressure and correction of hypokalemia are not the only goals of treatment for PA and prevention of organ damage is essential in these patients to prevent major cardiovascular complications and renal events[11].

This editorial will focus on the renal aspects of PA as the kidney is a key determinant of both adaptation to aldosterone-induced sodium and water retention, thereby acting as a rescue mechanism, and of clinical outcome of PA because renal function is critical for blood pressure response to treatment[12].

ALDOSTERONE-RELATED TISSUE DAMAGE: EXPERIMENTAL EVIDENCE

Exposure to aldosterone levels inappropriate for salt status or activation of mineralocorticoid receptors can cause renal tissue injury *via* mechanisms that are independent of blood pressure[13]. A series of elegant experiments that were conducted by Ricardo Rocha and coworkers demonstrated that in the kidney of uninephrectomized[14] and stroke-prone spontaneously hypertensive rats[15], aldosterone produces intrarenal vascular injury, glomerular damage, and tubulointerstitial fibrosis. Because animal studies consistently indicated that aldosterone causes renal tissue damage in the context of inappropriate salt status, it was suggested that untoward effects of high-salt intake are largely dependent on activation of mineralocorticoid receptors and that this activation might reflect increased oxidative stress[16]. Infusion of aldosterone in the presence of high-salt diet increases the expression of the renal nicotinamide adenine dinucleotide phosphate [NAD(P)H]-oxidase 4 (NOX4) and the subunit "p22phox", increasing the generation of reactive oxygen species (ROS) in the kidney. In these high-salt fed animals, administration of the mineralocorticoid receptor antagonist eplerenone, or the NAD(P)H-oxidase inhibitor apocynin, prevented aldosterone-induced increase in blood pressure, reduction of plasma nitric oxide levels, and increased urinary excretion of isoprostanes, a marker of oxidative stress[17].

Mineralocorticoid receptors with high affinity for aldosterone and cortisol have been demonstrated in epithelial and non-epithelial tissues. Under physiological conditions, most non-epithelial mineralocorticoid receptors are occupied by high concentrations of cortisol[18], whereas in epithelial tissues binding of cortisol to receptors is prevented by 11β-hydroxysteroid dehydrogenase (11β-HSD2), the enzyme that converts cortisol to the receptor-inactive hormone cortisone. In addition to the conversion of cortisol to cortisone, activity of 11β-HSD2 generates NADH from NAD and produces changes in the intracellular redox potential that might, in turn, inactivate the glucocorticoid-mineralocorticoid receptor complex[19]. It has also been demonstrated that aldosterone itself induces changes in the intracellular redox potential in many cell types[20] through an activation of the NOX1 catalytic subunit of the NAD(P)H-oxidase. Again, this aldosterone-related change in the redox potential is amplified by exposure to salt[21], leading to increased production of ROS and thereby to tissue injury. The mineralocorticoid receptor has also been demonstrated in brain, another non-epithelial tissue, particularly at sites in the anterior hypothalamus and brain stem. By acting on these sites aldosterone regulates salt appetite, sympathetic system discharge, water and electrolyte balance, and blood pressure. Sodium concentrations in the cerebrospinal fluid and the expression of the epithelial sodium channel (ENaC) in neurons are increased by administration of high-salt and aldosterone, respectively. Increase in intraneuronal sodium is mediated by increased ENaC-generated transport and stimulates generation of digitalis-like factors, thereby activating the local renin-angiotensin-aldosterone system and sympathetic outflow. Thus, aldosterone-induced sympathetic outflow resulting from the effects of the hormone on the central nervous system could contribute to maintaining high blood pressure[22]. In summary, in addition to the well-known effects of salt excess on epithelial swelling, vascular stiffening, and blood pressure increase, some effects of salt loading might depend on mineralocorticoid receptor activation and reflect, in various tissues including the kidney, increased oxidative stress.

KIDNEY IN PA

Evidence of beneficial effects of mineralocorticoid receptor antagonists was obtained in small clinical trials that were conducted in proteinuric patients with diabetic nephropathy[23] or chronic kidney disease caused by various renal condition[24]. In PA, cross-sectional evaluations have shown a high degree of variability in the prevalence of clinically relevant renal damage[25-30]. Initial kidney biopsy studies demonstrated only moderate damage in patients

with PA and reported prevalence of decreased kidney function in as little as 7% of patients with this endocrine disorder[26]. Similarly, a recent single-center study has reported 24-h creatinine clearance of less than 60 mL/min per 1.73 m^2 in only 7% of 56 patients with PA[30], whereas in the German Conn Registry, increased plasma creatinine concentration was found in a substantially higher percentage of patients[31]. In patients with PA, prevalence of overt proteinuria varied from 8%[26] to 24%[25], a disparity that could be explained by differences in duration and severity of disease. In a large, multicenter, Italian study[29], prevalence of microalbuminuria in patients with PA was twice that of patients with essential hypertension.

Fundamental information on the role of the kidney in PA has been obtained from two prospective studies, with short-term and long-term follow-up after treatment. Ribstein *et al*[32] reported a significant decrease in urinary albumin excretion after adrenalectomy in 25 patients with adrenal adenoma who were followed up for 6 mo. In a 9-year follow-up study of patients with either aldosterone-producing adrenal adenoma or idiopathic adrenal hyperplasia, we have shown that microalbuminuria is more likely to subside to normal levels after treatment than to progress to overt proteinuria[33]. In this study, restoration of normal albumin excretion was more frequent in patients with PA than in matched patients with essential hypertension and this effect appeared to be independent of blood pressure. Both these prospective studies have indicated that PA is characterized by partially reversible renal dysfunction, suggesting that albuminuria is, at least in part, a marker of a renal hemodynamic defect. In keeping with the findings of previous renal function studies[34], some of which were conducted in experimental settings[35], these two studies have demonstrated the presence of relative glomerular hyperfiltration in patients with PA as compared with appropriately matched patients with essential hypertension.

A recent analysis of 408 patients of the German Conn's Registry[31] and the results of the Taiwan Primary Aldosteronism Investigation study[36,37] have confirmed that glomerular filtration declines soon after treatment of PA and remains relatively stable thereafter. Moreover, evaluation of intrarenal Doppler velocimetric indexes has demonstrated significantly lower intrarenal vascular resistance in patients with PA in comparison with patients with essential hypertension, and reversal of the abnormal intrarenal hemodynamic pattern 1 year after treatment[38]. Thus, findings of longitudinal studies consistently indicate that renal dysfunction in PA is characterized by reversible glomerular hyperfiltration that is associated with decreased intrarenal vascular resistance and contributes to increased urinary albumin losses. The frequency of regression of microalbuminuria in PA suggests that urinary albumin excretion is, at least in part, a marker of functional rather structural renal changes[12]. On the other hand, long-term persistence of albuminuria in a substantial proportion of patients with PA[33] is associated with detectable baseline plasma renin levels[28,30] suggesting the coexistence of structural intrarenal vascular damage, presumably due to long-standing hypertension prior to treatment.

BLOOD PRESSURE AND RENAL OUTCOMES AFTER MANAGEMENT OF PA

The current treatment for aldosterone-producing adrenal adenoma is adrenalectomy, because surgery confers a greater possibility of cure and avoids the possible side effects of mineralocorticoid receptor antagonists. Chronic administration of these agents, however, is the treatment of choice in idiopathic adrenal hyperplasia[39]. Although PA is considered correctable, in many cases, hypertension may persist after surgical or medical treatment and only approximately one-third of patients are cured, defined as having blood pressure of less than 140/90 mmHg without the use of any antihypertensive drugs[28,40,41].

Most studies on the effects of treatment of PA on blood pressure have been conducted in patients with aldosterone-producing adrenal adenoma, and a cumulative analysis of initial case series indicated a rate of hypertension cure of 59% after unilateral adrenalectomy[3]. In the majority of these series, however, cure was defined on the basis of reaching a blood pressure of less than 160/100 mmHg. More recent evidence indicates that only approximately one third of patients treated for PA achieve a blood pressure of less than 140/90 mmHg without the use of additional antihypertensive drugs[3-5]. These estimates were obtained in retrospective investigations and are in agreement with the results of a recent prospective study of PA patients with either adrenal adenoma or idiopathic adrenal hyperplasia, 39% of whom had their blood pressure normalized by adrenalectomy or spironolactone, respectively, whilst the remaining 61% showed significant improvement (decrease of blood pressure by more than 20% and/or fewer antihypertensive agents taken to normalize values)[40].

Many studies have investigated the clinical and laboratory factors associated with resolution of hypertension after treatment of PA and have identified younger age, shorter duration of hypertensive disease, lack of family history of hypertension, milder preoperative antihypertensive therapy, lower plasma potassium, greater plasma or urinary aldosterone, and lower active renin[3-5,42-50] as relevant factors. We have recently demonstrated that higher pretreatment plasma renin is associated with less frequent normalization of blood pressure, together with smaller decline in albuminuria during follow-up (Figure 1), indicating that renin escape from suppression by excess aldosterone might be a marker of more severe hypertension-related renal damage[30].

It should be kept in mind that the key goal of treatment of all patients with high blood pressure as well as those with PA is the prevention of or recovery from organ damage, in order to decrease the risk of cardiovascular

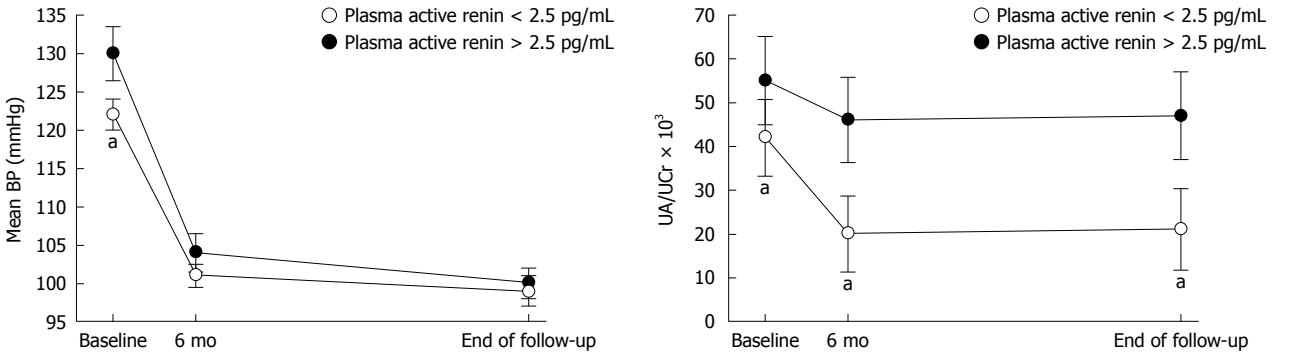

Figure 1 Values (mean ± SE) of mean blood pressure and albuminuria (urine albumin/creatinine ratio) in 56 patients who had primary aldosteronism and were categorized according to their plasma renin concentrations using the lower limit of detection for plasma active renin (2.5 pg/mL). Variables were measured at baseline and after treatment with adrenalectomy (n = 25) or mineralocorticoid antagonists (n = 31). Short-term and long-term measurements were done after 6 mo and after an average period of 6.2 years, respectively. [a]P < 0.05 *vs* patients with plasma active renin concentrations > 2.5 pg/mL. Modified by[30].

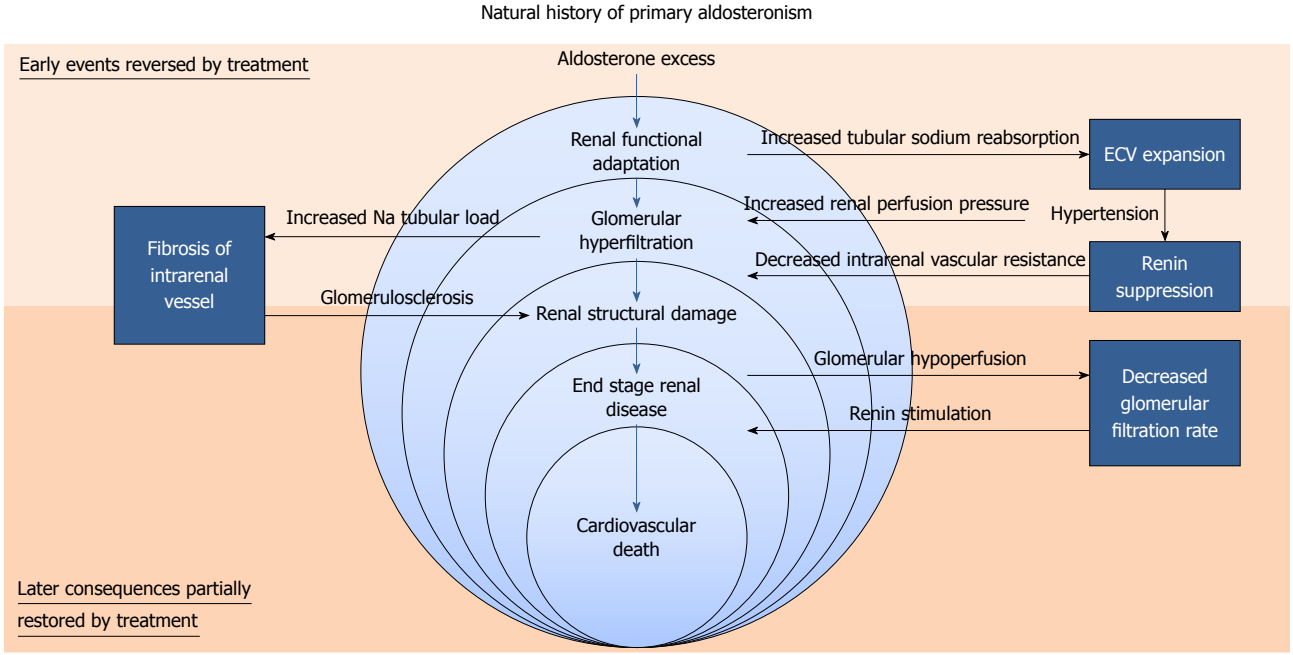

Figure 2 Proposed "course of events" in aldosteronism: from renal functional adaptation to end stage renal disease, cardiovascular events, and death.

events and renal failure. In this context, evidence linking, in the long term, treatment of PA with renal prevention is recent and refers thus far, to a single-center study in which renal outcomes have been compared in 54 patients with PA and 108 patients with essential hypertension who had comparable cardiovascular risk profiles[33]. Renal outcomes were assessed by measuring the rates of change of glomerular filtration and urinary albumin excretion. After an initial fall in creatinine clearance, due to correction of the aldosterone-induced intrarenal hemodynamic adaptation[38], subsequent declines in glomerular filtration in patients with PA (-1.15 mL/min per 1.73 m^2 a year) and primary hypertension (-1.06 mL/min per 1.73 m^2 a year) were comparable. Urinary albumin losses did not differ between patients with PA and essential hypertension during the long-term phase of follow-up. Separate analysis of renal outcomes in patients with PA who were treated with adrenalectomy or spironolactone did not reveal significant differences. These studies clearly demonstrate that, in patients with PA, renal impairment does not differ from that seen in patients with essential hypertension when the effects of excess aldosterone are permanently removed and that, in this context, both adrenalectomy and aldosterone antagonists are of considerable therapeutic value.

CONCLUSION

Today it is clear that PA causes a variety of cardiac, vascular, metabolic, and renal sequelae[10] that reflect the ability of inappropriately elevated aldosterone to induce tissue damage in addition to that caused by hypertension itself. However, in dealing with the role of the kidney in PA two distinct aspects need to be considered (Figure 2). On one hand, there are functional adaptations that are induced by increased tubular sodium reabsorption and

lead to increase of extracellular fluid volume, hypertension, increased renal perfusion pressure, and suppression of renin with decreased intrarenal vascular resistance[38]. These intrarenal hemodynamic changes cause glomerular hyperfiltration and increase sodium excretion, with escape from the tubular effect of aldosterone[30] and recovery of a steady state. At this stage of disease, the intrarenal hemodynamic adaptation is reversible and, by preventing progressive water and sodium retention, acts as a rescue mechanism. On the other hand, there is structural damage that involves primarily the intrarenal vessels and results from both persistent hypertensive insult and the direct untoward effects of aldosterone. This damage may take several years to develop, leading to decreased glomerular perfusion and stimulation of renin release that escapes from suppression by excess plasma aldosterone and subsequent volume expansion[30]. In this context, lack of complete renin suppression in patients with PA could be the hallmark of more advanced kidney disease with specific involvement of the intrarenal vessels[12]. At this stage of disease, the kidney becomes the key determinant of the clinical outcome of PA, because kidney function is critical for blood pressure response to treatment.

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OBSERVATION

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A survey of recent reports on ambulatory blood pressure monitoring

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Abstract

This article is a review of 25 publications on ambulatory blood pressure monitoring (ABPM) and the importance of its results in everyday clinical practice. These studies, published in 2008-2011, were selected from the Scopus database, but are also available in Pubmed. They were prepared by researchers from around the world, concerned with the problems of proper control of blood pressure (BP), and of abnormalities in the circadian pattern of BP in patients with arterial hypertension, diabetes mellitus or renal failure. In the first part of this article, I analyse publications focused on some nuances in the methodology of ABPM and recommend ways to avoid some traps, related not only to the individual patient but also to the device used and the technical staff. The next section is devoted to the advantages of ABPM as a diagnostic tool which enables clinicians to learn about patients' BP during sleep, and emphasizes the practical implications of this information for so-called chronotherapy. This section also presents some new studies on the prognostic value of ABPM in patients with cardiovascular (CV) risk. Some recent articles on the results of various methods of pharmacological treatment of arterial hypertension in different age groups are then described. The observations presented in this article may be helpful not only for researchers interested in the chronobiology of the CV system, but also for general practitioners using ABPM.

Key words: Ambulatory blood pressure monitoring; Arterial hypertension; Blood pressure; nondipping; Pharmacological treatment

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INTRODUCTION

Although it has been almost 50 years since Maurice Sokolow first conceived, and then constructed, an apparatus for ambulatory blood pressure monitoring (ABPM), it has to be emphasised that initially this device was "a toy in the hands of scientists" rather than a routine diagnostic tool. It is only in the last 20 years, probably because of the increased popularity and availability of this equipment, that the number of publications describing experience with this method has grown year after year. While in the early 1990s only a few dozen publications on this topic were added to the databases of medical journals each year, in the 21st century almost one hundred new reports appear annually. The present paper is a review of those studies on ABPM from the last 4 years which are,

in the author's view, the most interesting from a practical point of view. The studies have been grouped thematically.

METHODOLOGICAL TRAPS, OR HOW TO USE ABPM EFFECTIVELY

When it is set to 15 min intervals during the day and to 30 min intervals in the night, the device for ABPM takes about 100 measurements in one test session. The results of the monitoring are regarded as reliable when at least 90% of the results meet the criteria of properly taken measurements.

Researchers from the Family Care Center, University of Iowa Hospitals and Clinics (USA), decided to specify patient profiles which are associated with an insufficient quality of ABPM measurements. In order to define the profile of a patient for whom the percentage of valid readings was too low, the researchers analyzed 530 patients (age range 14-90 years) who underwent ABPM in 6 consecutive years. The analysis included age, sex, weight, height, body mass index (BMI), occupation, the distance from their home to the Clinic, the existence of diabetes mellitus or renal failure, as well as the values of arterial blood pressure (BP) measured by an office sphygmomanometer. The studied group was divided dichotomously into two: patients in whom the percentage of valid measurements was between 0% and 79%, and patients in whom that percentage was 80% and more (the threshold of a satisfactory quality of measurement was reduced by the authors of the study by 10%). In 84.7% of the patients, technically satisfactory readings were obtained, and analysis of the characteristics of patients in whom the percentage of artefacts, invalid readings, or measurements with technical problems was higher than 20%, indicated that diabetes mellitus, renal failure, and increased BMI are indicators which were associated with incomplete circadian ABPM session results. The authors of this study posed the question of whether individualisation or adaptation of this method, geared especially towards the patients demonstrating the above-mentioned factors, would improve the accuracy of the results of ABPM[1].

Another methodological problem is connected not with the device, but with the human input to the process of conducting this examination. This concerns the precision with which the clinic technician inputs the patient's actual sleep time during the ABPM session. The importance of this issue was demonstrated in patients with type 1 diabetes by Delaney *et al*[2]. They compared the frequency of diagnosing the nondipper profile between a group where the actual sleep times were used and a group where preset sleep times were input into the software for evaluating the pressure profile. The diabetic patients for whom preset sleep times were used were significantly more frequently diagnosed with a nondipper profile than those for whom actual sleep times were given. When, in a second round of monitoring, the reproducibility of the nondipping phenomenon was evaluated in the group with preset sleep times, it was apparent that, after actual reported sleep times were input into the software, only 36% of the patients actually showed disorder of the circadian rhythm of BP. The researchers recommend at least two rounds of BP monitoring in patients who were initially diagnosed with a nondipper profile, since conclusions from the first monitoring may have been the result of a methodological error.

ABPM is very time-consuming, and hence there is a temptation to ask to what extent shorter monitoring times are representative of the BP determined from a full 24-h ABPM session. In the study by Ernst *et al*[3], doctors and statisticians evaluated more than one thousand ABPM examinations. After excluding the first hour of recording, the researchers divided these into 4-, 6-, and 8-h sessions, in order to compare the mean systolic BP over the shortened periods with the full 24-h session mean. Although the reduction of the BP monitoring to 6 h gave a mean BP value which was lower by about 5.41 mmHg, still, the shorter monitoring time produced values relatively close to the patient's mean obtained from a full 24-h session.

In 2011, Ernst *et al*[4] analyzed the same database of ABPM recordings in order to examine correlation of 6-h ABPM sessions with the results of full (24-h) BP monitoring across four clinical indications of referral, namely: (1) borderline hypertension; (2) evaluation of BP control on mono or dual therapy; (3) suspicion of white-coat hypertension; and (4) resistant hypertension. They found that using the 6-h systolic BP threshold of 137 mmHg for patients with indications of referral 1, 2, and 3 achieved high correlation for sensitivity and specificity (over 0.8), and using the threshold of 133 mmHg for patients with indication of referral 4 produced even higher values: at 0.93 and 0.83, respectively[4].

In clinical practice it is rare for patients to undergo both electrocardiogram (ECG) monitoring and BP monitoring simultaneously. However, for a group of 239 patients in this not very comfortable situation, researchers from the University of Bonn (Germany) analysed changes in the ST segment in 24-h ECG Holter monitoring, whilst also monitoring circadian variability in BP[5]. In addition, the study analyzed ST segment depression induced in an exercise test on a cycle ergometer. ST-segment depression that met the criteria of myocardial ischemia was recorded in 29% of patients. In 7.6%, ST depression occurred only during the exercise test, in 9.6% only during the Holter monitoring, and in 11.8% it was detected by both methods. In the last subgroup, significantly lower threshold levels of BP and heart rate were observed at the onset of ST depression recorded in Holter monitoring during routine daily activities in comparison with the changes induced on a cycle ergometer. The results were 148 (Holter) mmHg *vs* 188 mmHg (ergometer) for the pressure, and 120/min *vs* 93/min for the heart rate, respectively. Although in several earlier studies it was suggested that Holter monitoring can partly replace an exercise test for the detecting of ischemic heart disease, in this study, where ABPM was also

used, it was shown that these two methods do not replace but complement each other.

Kayrak *et al*[6] from Selcuk University (Turkey) analyzed the importance of exaggerated BP response during exercise in diagnosing masked hypertension (normal BP in office measurements, elevated values at night). They found that, when patients performed an exercise test while undergoing ABPM, 41% of patients with this type of reaction to physical effort have masked hypertension. The authors therefore suggested that patients in this group should receive closer follow-up for hypertension[6]. Another condition associated with transient elevation of BP is the application and removal of the device for ABPM. As demonstrated by Yanovski *et al*[7] from the University of Pennsylvania (USA), this phemomenon is present not only in patients with hypertension (treated or untreated) but also in normotensive ones. The authors suggested that this psychophysiologic reaction should no longer be regarded as an artifact and ignored, and recommended the inclusion of the data from the initial and final measurements in the analysis of ABPM results[7].

Standard deviation of serial BP measurements is a parameter which, in clinical trials, is calculated both for ABPM and for repeated casual office BP measurements (CBP). In the case of paediatric patients, for whom the frequency of occurrence of arterial hypertension is low and the effect of "white coat" syndrome is strong, the question arises whether ABPM would not be a more ethical form of checking the efficacy of antihypertensive drugs, and whether using this method in multicenter trials would allow researchers to reduce the cohort size, while maintaining the validity of the results.

A group of paediatricians-nephrologists from 9 countries who conducted clinical trials on the efficacy of ramipril in children with arterial hypertension tested the above-mentioned hypothesis, and analyzed the values of standard deviation for BP measured by means of the traditional method (CBP measurement) and also by ABPM. The efficacy of ramipril was proved by both methods but, as was to be expected, the divergence of BP measurements (as well as standard deviation) was much greater with the traditional method. Statistical simulation has shown that the use of ABPM in multicenter clinical trials on the efficacy of antihypertensive drugs in children would allow reduction of the number of patients required to be randomized to active treatment or to placebo by 75%[8].

ABPM AS A PROGNOSTIC INSTRUMENT, OR TECHNOLOGY ENTERS THE BEDROOM

In recent literature there are many studies concerning the prognostic value of the results of ABPM. These studies concern not only the patients of doctors with narrow specializations [e.g., nephrologists who take care of patients after kidney transplantation or electrocardiologists who control patients with implanted cardioverter-defibrillators (ICD)], but also patients from the daily practice of internists and family doctors, who are under medical care because of common diseases such as arterial hypertension and diabetes mellitus.

Krmar *et al*[9] from the Karolinska University Hospital (Sweden) evaluated the possibilities for early diagnosis of arterial hypertension in children after a kidney transplantation (the mean age of the recipients was 10 years) who were followed up for approximately 4 years (4.3 ± 2.2). They compared the frequency of diagnosing hypertension in this high-risk group following office BP measurements with the more recent period when regular ABPM performed at least once a year became the routine policy. In the "historical" period (the authors' own term), hypertension was diagnosed on average 6 years after the transplantation, whereas with regular ABPM the decision to start or intensify antihypertensive treatment was made much earlier in 27 out of 37 cases (73%), significantly improving control over this risk factor in this young age group[9].

The study by Paoletti *et al*[10] from Genoa (Italy) also concerns patients after kidney transplantation. Here the patients were older renal transplant recipients (aged 28-71 years), and the aim of the study was to examine the possibilities of an early diagnosis of renal graft damage. The researchers compared the classic markers of an adverse course after a kidney transplant (serum creatinine, daily proteinuria, triglycerides, immunological markers) with the results of 24-h ABPM. It turned out that the values of diastolic BP during the night and the initial creatinine concentrations were the only strong predictors of creatinine level a year after the surgery, while daytime systolic BP allowed them to predict intensified daily proteinuria. The authors concluded, somewhat surprisingly, that ABPM is the most reliable diagnostic method available to evaluate the course of the disease in renal transplant recipients. Similarly, Beltrán *et al*[11] from Valencia (Spain), observing the results of ABPM among kidney transplant patients, reported that "poorly controlled hypertensives" were older (54 ± 9 years *vs* 45 ± 13 years) than "well controlled hypertensives", received grafts from older donors (56 ± 15 years *vs* 45 ± 1 7 years), had higher serum creatinine concentrations (1.7 ± 0.5 mg/dL *vs* 1.4 ± 0.4 mg/dL) and more advanced proteinuria (0.3 g/d *vs* 0.18 g/d). The large prevalence of uncontrolled nocturnal hypertension had a very strong impact on the abnormal result of ABPM in these patients[11].

A further attempt to use ABPM results as a prognostic tool was made jointly by gynecologists and hypertensiologists from two Polish medical centers (Kraków and Gdańsk). The article by Liro *et al*[12] describes a group of 123 pregnant women with gestational hypertension (in most cases, this was their second pregnancy). For these women, the ABPM result was prognostic of the risk of premature delivery, because increased BP values during this examination were inversely correlated with the duration of the pregnancy and the child's birth weight[12].

Stratification of the risk of death is one of the most

important challenges for electrocardiologists who qualify patients for ICD in cases of dilated cardiomyopathy. An interesting method of death risk evaluation, proposed by the group of Antonini *et al*[13]. from Rome (Italy), was tested on a group of 105 patients after the ICD implantation. All the patients in this study had left ventricular ejection fraction ⩽ 30%, and at 12-mo follow-up this parameter had no prognostic value for end-points such as death or hospitalization because of exacerbation of heart failure. Cox regression analysis revealed statistical significance for the prognostic value of the combination of the patient's age and the mean values of the 24-h systolic and diastolic BP. A prognostic index calculated in this simple manner was, therefore, proposed: (120 - age) + (mean 24-h systolic BP + mean 24-h diastolic BP).

Using this index it was shown that 61% of patients in whom it was ⩽ 220 had end-points during the follow-up, while the percentage was significantly lower (12%) for patients whose index was > 220[13].

The next group of studies concern patients with diabetes mellitus and arterial hypertension who are seen on a daily basis by a larger number of doctors.

A Japanese-American team Eguchi *et al*[14] tested the hypothesis that short-term BP variability and an abnormal circadian BP profile evaluated by ABPM help to predict the risk of cardiovascular (CV) diseases in patients with type 2 diabetes mellitus. Three hundred such patients, who underwent ABPM, were followed for 50 ± 20 mo. The researchers established the abnormalities of their initial profile (nondipper, reverse-dipper, or excessive morning BP surge) and calculated the standard deviations of ABPM, separately for the hours when the patients were awake and for the time when they were asleep. This study is different from previous publications in that the authors regard excessive diastolic BP variability during sleep-time and the mean diastolic BP value at night, and not the nondipper, or reverse-dipper profile or excessive morning BP surge, as parameters significantly correlated with CV episodes[14]. Similar conclusions can be found in the paper by Leitão *et al*[15] from Brazil. They compared the prognostic value of an abnormal circadian BP profile with that of mean BP values during the day and at night, in order to assess the risk of microvascular target organ damage diagnosed by means of ophthalmoscopy, through increased proteinuria, or during echocardiographic examination of left ventricular hypertrophy in 270 patients. Again, it was not the circadian profile, but the night-time BP values that were correlated with the presence of hypertensive angiopathy, whereas cardiac hypertrophy and increased microalbuminuria were correlated more strongly with elevated systolic BP means than with night/day BP ratios[15].

The work by Bouhanick *et al*[16] from Toulouse (France), also shows how important night-time BP values are for determining the risk of CV death, myocardial infarction or stroke in patients with type 2 diabetes and arterial hypertension. These researchers compared a group of reverse-dippers with patients classified on the basis of ABPM as nonreverse-dippers ("others") in terms of CV complications. Ninety-seven patients were followed up for a median period of 5.5 years (and after a median period of 2 years and 7 mo they had undergone another ABPM). More than half of the patients (53%) who were classified as reverse-dippers after the first ABPM experienced CV events, whilst these events were significantly less frequent in 29% of patients. The most important conclusion from that paper is, however, that there were significant differences between the patients as regards mean night-time systolic BP. In the group of reverse-dippers this was 148 ± 23 mmHg, compared to 142 ± 19 mm among the nonreverse-dippers. The researchers calculated that an increase in the mean night-time systolic BP of 10 mmHg was associated with a 35% increase in the risk of a CV event in diabetic patients with hypertension[16].

Does this mean that in patients with type 2 diabetes we should administer ABPM more frequently before any therapeutic decisions are made, since night-time BP measurement provides us with so much essential information? Conversely, one might ask whether an oral glucose tolerance test should be administered more frequently in normotensive, non-diabetic subjects with decreased nocturnal BP reduction (nondippers), since Li *et al*[17] described a significantly higher prevalence of the nondipping pattern in subjects with impaired glucose tolerance (77.4%) when compared with those presenting normal glucose tolerance (52.8%).

The author of the next two articles on the prognostic role of the results of ABPM seems to have been guided by the principle that there are no healthy people, only those who have not been diagnosed. Soylu *et al*[18] from the Meram Medical School of Selcuk University in Konya (Turkey) examined people who considered themselves healthy (the so-called normotensives), and tried to find a correlation between an abnormal circadian BP profile and the echocardiographic parameters of left ventricular diastolic function and cardiac structural changes. He demonstrated that the nondipper profile was associated with diastolic function disorders and a tendency for longer isovolumic relaxation time[18]. In a later publication, also on normotensives, the same author demonstrated that an insufficient reduction of systolic BP at night-time and an increased morning BP surge (after waking up) lead not only to a significantly higher left ventricular mass index, but also to an increased urinary albumin excretion. The group of patients cited here suggests that an effective pharmacological attempt to restore the normal circadian rhythm of the BP could reduce the risk to the target organ, at least in the context of individuals with arterial hypertension[19].

ABPM AS A MEANS OF CONTROLLING THE EFFECTS OF TREATMENT, OR WHICH DRUG TO CHOOSE

Which drugs should then be used to restore the normal

circadian BP rhythm? It seems natural to reach for the hormone of the biological clock - melatonin. In our own study we established that in patients with coronary artery disease and an abnormal BP profile, melatonin can restore the dipper profile in only 35% of patients diagnosed as nondippers at the beginning of the observation. Doctors considering giving melatonin to patients of this type, who often take several antihypertensive drugs, must be warned that increasing the ratio of the difference between the mean systolic BP value during the day and at night-time can be achieved not only through lowering sleep-time systolic BP but also through increasing the mean active BP[20]. Researchers focusing on the chronobiology of the circulatory system have emphasized that the time at which the medication is taken is an important factor attempting to improve the circadian BP profile. This aspect of the problem was studied, by Takeda *et al*[21] from Japan who confirmed the beneficial effect of giving long-acting antihypertensive drugs in the evening (as opposed to giving it in the morning) not only on the normalization of BP values, but especially on the restoration of the physiological rhythm of this parameter[21].

Researchers from Spain and Switzerland used ABPM to evaluate the effects of missing one dose of antihypertensive medication in previously untreated patients with mild hypertension who had started their therapy only recently. According to statistics, some 15% to 20% of patients with hypertension forget to take their medication approximately 3 times a month. The comparison was between valsartan 160 mg/d taken in the morning and enalapril 20 mg/d also taken on waking. Unlike enalapril, valsartan was shown to be a drug with a more sustained effect, and with no significant influence of one missed dose on the BP level[22].

A similar comparison of the angiotensin receptor blocker, telmisartan, and the angiotensin-converting enzyme inhibitor, ramipril, was described in the article by Williams *et al*[23]. The observation of two groups of hypertensive patients (each group consisting of more than 800 patients) randomized to telmisartan (80 mg) or ramipril (5 or 10 mg) focused on improving the mean 24-h systolic BP and the diastolic BP during the final 6 h of the monitoring. These trials, known under the acronyms PRISMA I and PRISMA Ⅱ, favoured sartan, as a drug with a longer, more sustained effect, unchanged throughout the 24-h period[23].

What can we say about the efficacy of two types of sartans used in combination therapies in hypertensive patients over 80 years old, patients who are largely ingnored in clinical trials? Fogari *et al*[24] used BP monitoring to compare the effects of valsartan/amlodipine combination treatment *vs* irbesartan/hydrochlorothiazide combination for 8 wk in such patients. Valsartan with amlodipine turned out to be equally effective in reducing BP, but offered additional advantages in terms of less pronounced BP variability related to changes in body position, and fewer metabolic disorders, mainly hyperurycemia[24].

CONCLUSION

In conclusion, I would like to describe the results of a study which is fascinating in that it involved a very large group of people (745 volunteers) and covered a very long observation period, thereby yielding a lot of data. Between 1989 and 2004 the researchers collected results of arterial BP monitoring in children (the mean age at the beginning of the observation was approximately 14), who, before they reached early adulthood (approximately 20 years of age), had undergone multiple repeated ABPM[25]. On average each volunteer had undergone about 12 ABPM sessions. In the analysis of the results the authors used the so-called tracking coefficient, which can be described as "the coefficient of repeating the first result". Values of this coefficient in the range 0.3-0.59 were considered to indicate degree of stability of the given parameter, and values < 0.3 suggest very little stability of the measurement. While it was shown that the mean results of both pulse pressure measurement and day-time and night-time BP measurements were predictably reproducible throughout the years, the tracking coefficients for the circadian BP variability turned out to be surprisingly low. In order to evaluate circadian BP variability, the researchers used three methods: (1) The traditional division into dippers and nondippers depending on the ratio of the mean day/night systolic BP higher than 10%; (2) Calculation of the absolute difference between the mean day-time BP and the mean night-time BP; and (3) Expression of night-time decrease in BP as a percentage of day-time BP.

Each of these methods showed an unsatisfactorily low tracking coefficient. The reproducibility of the results for dippers *vs* nondippers has for years been a moot point among researchers dealing with the chronobiology of the circulatory system. However, previously no one had gathered a substantial amount of data about multiple ABPM measurements in such a large population. If the results of this study were to be confirmed in a group of adults or in groups of patients with arterial hypertension or with ischemic heart disease, then the division of patients into dippers and nondippers according to the current criteria would be seriously undermined if not invalidated, as signaled by the authors of the studies described in the earlier sections of this article.

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REVIEW

Adipose tissue in the pathophysiology of cardiovascular disease: Who is guilty?

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Abstract

Epidemiological evidence has shown how abdominal obesity is closely associated with the development of cardiovascular disease. It has been demonstrated that patients with extensive adipose tissue usually have other concomitant cardiovascular risk factors, such insulin resistance, hypertension and dyslipidemia. Moreover, obese patients have a significantly higher risk of developing thrombophilic events compared with the non-obese. Thus, obesity is actually considered an independent cardiovascular risk factor. The pathophysiological mechanisms responsible for the association between obesity and cardiovascular disease remain largely unknown. However, it has been postulated that obese patients have an "inflammatory milieu" responsible for their metabolic disorders and vascular disease. In this context, adipocyte-derived molecules with inflammatory activity might play a pivotal role in the development of these mechanisms. In the present report, we provide an updated overview on the molecules produced by adipose tissue that are potentially involved in cardiovascular pathophysiology.

Key words: Adipokines; Atherosclerosis; Cardiovascular disease; Inflammation; Obesity; Thrombosis

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INTRODUCTION

Nowadays, obesity is considered an emerging and rapidly expanding disease, mainly in industrialized countries. In fact, it can be considered a typical "disease of the affluent"[1]. The World Health Organization estimates that more than 1 billion people are overweight and 300 million are obese in the world[2]. For many years, epidemiological evidence has shown that abdominal obesity is closely associated with the development of cardiovascular disease[3,4]. Specifically, patients with extensive adipose tissue have a higher incidence of other cardiovascular risk factors, such as insulin resistance, hypertension and dyslipidemia[5]. Interestingly, obese patients have a thrombophilic risk 1.5 to 2.5 times higher than the non-obese. Taken together, these observations have suggested that obesity might be considered as an independent cardiovascular risk factor[6]. Despite these clinical observations, the pathophysiological mechanisms responsible for the association between obesity and cardiovascular disease remain largely unknown. However, it has been recently postulated that obese patients have an "inflammatory milieu" responsible for their metabolic disorders and vascular disease[7]. In this context, adipocyte-derived molecules with inflammatory

activity might play a pivotal role in the development of these inflammatory mechanisms. In the present report, we provide an updated overview of the molecules produced by adipose tissue potentially involved in cardiovascular pathophysiology.

ADIPO(CYTO)KINES

The cells of adipose tissue, adipocytes, are no longer considered only as fat storage cells. They are considered as cells able to produce and secrete several substances with biological activity, known as "adipokines"[8,9]. The biological functions of adipokines are still partially unknown; however, they seem involved in the regulation of many physiological processes, such as appetite regulation and energy balance, lipid metabolism, blood pressure, insulin sensitivity, inflammation, haemostasis and angiogenesis[10]. It is known that, in the plasma of patients with obesity or metabolic syndrome, increased levels of some adipokines can be measured, suggesting that these adipocyte-derived substances might be considered as novel biomarkers and regulators of the metabolic syndrome[11].

It has been observed that adipocytes belonging to the adipose tissue of obese patients can synthesize and secrete several adipokines. Moreover, this tissue appears to be infiltrated by inflammatory cells[7]. Interestingly, adipokines secreted by visceral fat have a more remarkable biological activity than adipokines released by subcutaneous fat[7]. It was also shown that weight loss and exercise could ameliorate the inflammatory milieu of patients with metabolic syndrome by modulating their adipokine profile[11,12]. To date, the adipokines actually discovered can be divided into four groups: (1) adipokines with metabolic functions; (2) adipokines with pro-inflammatory functions; (3) adipokines components of the extracellular matrix; and (4) adipokines with pro- angiogenic and pro-mitogenic action[11]. However, some of them fall out of this schematization and can be placed transversely across multiple categories. In addition, only some of these molecules appear to play an active role in cardiovascular pathophysiology.

ADIPONECTIN

Adiponectin is a 247 amino acid protein with a globular carboxyl-terminal domain and an amino-terminal collagen-like domain[13]. This adipocytokine and complement factor 1q has a similar structure[14]. In humans, the adiponectin gene is located on chromosome 3q27[15]. This adipokine seems to exert protective effects on the cardiovascular system[16]. In fact, patients with a high atherosclerotic burden have low plasma levels of adiponectin[17]. Moreover, it has been demonstrated that low plasma levels of this adipokine are closely related to the progression of coronary atherosclerosis in patients with angina pectoris[18]. Finally, it has been observed that women with low plasma levels of adiponectin have impairment of the coronary flow reserve[19]. Although adipocytes are the main source of adiponectin, patients in which adipose tissue are largely represented, such as the obese and those affected by metabolic syndrome or diabetes mellitus, have low measurable plasma levels of this adipocytokine[20]. In the plasma, three different oligomers of adiponectin have been isolated, each one with a specific biological function[21]. We can identify: (1) low molecular weight (LMW) oligomers, constructed by three molecules of adiponectin; (2) middle molecular weight (MMW) oligomers, formed by six adiponectin fractions; and (3) high molecular weight (HMW) oligomers constituted by 12 -18 molecules of adiponectin[22]. Then, another oligomer has been recently isolated in which three molecules of adiponectin are bound to albumin (Alb-LMW)[23]. In humans, MMW and LMW adiponectin represent 25% while HMW adiponectin represents 50% of whole circulating adiponectin[23]. Since plasma levels of HMW appear to be closely related to insulin sensitivity, it has been suggested that HMW is biologically active[24,25]. Two specific adiponectin receptors have been identified: AdipoR1 and AdipoR2. Binding of adiponectin to the AdipoR2 receptor increases energy consumption and improves fatty acid oxidation. Moreover, when adiponectin binds the AdipoR2 receptor, pro-atherosclerotic processes such as oxidative stress and inflammation are significantly inhibited[26]. In particular, in the atherosclerotic plaques, adiponectin should modulate the inflammatory response by down-regulating the expression of pro-inflammatory mediators, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6 and interferon (IFN)-c, and by up-regulating anti-inflammatory molecules, such as the antagonist receptor for IL-1[27]. As reported above, *in vivo*, adiponectin increases energy consumption and oxidation of fatty acids in the liver and muscles. These phenomena contribute to reducing triglycerides levels in these tissues and improving insulin sensitivity[28]. In endothelial cells, adiponectin induces the activation of endothelial nitric oxide synthase (eNOS) and stimulates nitric oxide production[29]. Moreover, adiponectin inhibits the oxygen free radical production and ameliorates the endothelial function in mice genetically modified to develop hyperlipidemia and atherosclerosis[30].

Several experimental studies have clearly demonstrated that adiponectin plays a protective role for the cardiovascular system since it is able to interfere with the early steps of atherosclerotic disease. In particular, it has been shown that adiponectin deficiency increases leukocyte-endothelium interactions *via* up-regulation of endothelial cell adhesion molecules (CAMs) *in vivo*[31]. Conversely, the expression of adhesion molecules is reduced when increased levels of adiponectin are measurable[32]. Moreover, adiponectin suppresses smooth muscle cells proliferation[33] and inhibits lipopolysaccharide-induced adventitial fibroblast migration and transition to myofibroblasts *via* the AdipoR1-AMPK-iNOS pathway[34]. Again, adiponectin suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages[35]. Finally, this adipocytokine reduces lipid accumulation in macrophage foam cells[36] and is able to reduce atherosclerosis in apolipoprotein E-deficient

mice[37]. Of note, adiponectin seems to play an important role in modulating the inflammatory network involved in the pathophysiology of cardiovascular disease because it regulates the expression of several important chemokines, such as IP-10, Mig and I-TAC, which bind to the chemokine receptor CXCR3, an important regulator of chemotaxis of lymphocytes within the atherosclerotic plaque[38]. The protective role played by adiponectin has also been confirmed by recent studies showing that the adiponectin receptor is detectable on platelets, thus suggesting that this adipocytokine acts as an endogenous antithrombotic factor[39].

LEPTIN

Leptin is a polypeptide consisting of 167 amino acids, encoded by the "ob" gene and implicated in the regulation of body weight and energy balance[40]. Experimental and clinical evidence has shown that this peptide might be involved in the pathophysiology of metabolic syndrome[41]. In fact, elevated leptin plasma levels are usually detectable in the plasma of obese patients[42]. In this context, the relationship between obesity, elevated plasma levels of leptin and cardiovascular disease appears of particular interest. Several clinical studies have shown that patients with increased plasma concentrations of leptin are at high risk of developing myocardial infarction[43] and stroke[44]. In addition, elevated serum levels of leptin were measured in patients with myocardial infarction with ST elevation[45]. Finally, a large prospective study on leptin and cardiovascular risk, the West of Scotland Coronary Prevention Study, confirmed that leptin is an independent predictor of coronary events[46]. This adipokine has recently been identified as a good prognostic marker of future cardiovascular events in patients with angiographically proven atherosclerosis[47]. Elevated leptin baseline levels are associated with increased risk of cardiac death, new myocardial infarction, stroke and coronary revascularization, even in patients without diabetes[47]. Hyperleptinemia is closely associated with in-stent restenosis in patients undergoing coronary stenting[48]. Moreover, the ratio of leptin:adiponectin seems to be directly correlated with the magnitude of the intima-media thickness of the common carotid artery, a good index of subclinical atherosclerosis[49]. Finally, it has been suggested that leptin, by stimulating the sympathetic nervous system, might also play an important role in the pathophysiology of hypertension[50]. These clinical observations have been supported by experimental studies which have strongly reinforced the hypothesis that leptin might be involved in the pathophysiology of cardiovascular disease. Leptin seems to be able to modulate platelet aggregation[51] and arterial thrombosis[52,53]. In a recent paper, it has been demonstrated that leptin, at concentrations usually measurable in the plasma of patients with acute coronary syndrome, induces a pro-atherothrombotic phenotype in human coronary endothelial cells through the expression of tissue factor (TF) and CAMs[54]. Moreover, leptin can induce the expression of TF in human peripheral blood mononuclear cells[55].

The progression of atherosclerotic plaques might be modulated by leptin. Treatment of apo-lipoprotein E deficient mice with leptin causes faster progression of vessel atherosclerosis and increases the amount of calcium in the vessel wall[56]. In addition, it has been shown that treatment of hyper-lipidemic mice with recombinant leptin increases the atherosclerotic burden and promotes a faster thrombus formation[53]. Interestingly, leptin deficiency suppresses progression of atherosclerosis in apoE-deficient mice[57]. Recently, it has been demonstrated that leptin stimulates the production of C-reactive protein (CRP) in human coronary endothelial cells[58]. Since it has been previously evidenced that CRP induces vascular thrombosis[59], taken together, these observations suggest that leptin might promote the development of the atherosclerotic disease and that it might be involved in the pathophysiology of acute coronary syndromes.

RESISTIN

Resistin is a cysteine-rich protein of 12.5 kDa, consisting in humans of 108 amino acids: 17 amino acids form the N-terminal signal sequence, 37 in the variable portion and the remaining in the constant area at the C-terminal. Its gene is located on chromosome 19. Recently, a family of resistin-like molecules (RELMs) have been described. These polypeptides consist of 105-114 amino acids and are composed of three domains: a signal sequence at the N-terminal, a variable central portion and a highly conserved C-terminal. RELM α is secreted mainly by adipose tissue, while RELM-β is expressed only in the gastrointestinal tract and in neoplastic cells, suggesting a possible role in cell proliferation. RELM-γ, recently discovered, was found in hematopoietic tissue, where it is supposed to have a cytokine-like activity. In rodents, adipocytes are the main source of resistin, while in humans, macrophages have this function[60]. Initially, this adipokine was proposed as a potential link between obesity and diabetes by modulating the mechanisms responsible for insulin resistance[61]. Then, experimental evidence *in vivo* and *in vitro* has shown that resistin is able to trigger the mechanisms involved in inflammation[60]. In addition, plasma levels of resistin appear to be closely correlated with other markers of inflammation, such as TNF-α, type 2 soluble receptor for TNF-α and IL-6[62-64]. Of note, patients with acute coronary syndrome have resistin plasma levels significantly higher than patients with stable angina and healthy controls[65]. Then, it was also shown that resistin might be an independent predictor of coronary atherosclerosis in humans[62-64]. Finally, since plasma resistin is associated with myocardium injury in patients with acute coronary syndrome, it has been proposed as a marker of ischemic injury[66]. Recent experimental evidence has indicated that resistin promotes endothelial dysfunction. In fact, it in-

duces expression of adhesion molecules and cytokine in human endothelial cells[67]. In addition, it influences the expression of PI3Kp85 and stimulates the release of plasminogen activator inhibitor 1, von Willebrand factor and endothelin[68]. Again, resistin inhibits the expression of eNOS. Finally, recent studies have shown that this molecule is able to promote proliferation and migration of smooth muscle cells through the activation of ERKs and PI3K kinase[69,70]. In a recent *in vitro* study, it has also been shown that resistin induces the synthesis and expression of active TF in human coronary artery cells[71].

TNF-α

TNF-α is another important chemical mediator involved in the progression of atherosclerotic disease[72]. It has pro-inflammatory activity and is produced mainly by inflammatory cells, such as monocytes and macrophages. This molecule is actively involved in the modulation of inflammatory and autoimmune diseases. Adipose tissue of animals used as experimental models of obesity and type 2 diabetes has increased expression of TNF-α[73]. Similarly, elevated levels of TNF-α have been detected in adipose tissue and plasma of obese patients. Interestingly, TNF-α plasma levels are closely related to the extent of visceral adipose tissue, while weight loss and lifestyle changes reduce these levels[74]. TNF-α has been isolated in atherosclerotic plaques and it seems to be a marker of plaque growth[75-77]. The role played by this pro-inflammatory molecule was also highlighted by elegant experiments in mice genetically modified to be deficient in expression of TNF-α: these animals showed less atherosclerosis compared to the same animals not genetically modified. In addition, these animals showed a poor inflammatory profile with low levels of IL-1β, IFN-γ, ICAM-1, VCAM-1, MCP-1, GM-CSF and nuclear factor (NF)-κB[78]. TNF-α also appears to be able to regulate the expression of lectin-like type 1 receptor for oxidized LDL, an important facilitating atherosclerosis mediator in various cell types, including endothelial cells and macrophages[79].

IL-6

IL-6 is another pro-inflammatory cytokine with plasma levels closely related to the amount of visceral fat[80]. In fact, obese patients have elevated plasma levels of IL-6 which can be reduced by weight loss[74]. It is estimated that the adipose tissue is responsible for the production of about one third of the circulating levels of IL-6[80] and it has been hypothesized that the secretion of IL-6 in obese individuals contributes to metabolic dysfunction. In fact, plasma levels of IL-6 can be considered predictive for the development of type 2 diabetes and, in turn, high levels of this cytokine are detectable in diabetics[81]. IL-6 plays an important role in the pathophysiology of atherothrombosis: it modulates the release of pro-inflammatory cytokines and of other pro-thrombotic mediators, promotes lipoprotein oxidation, activates matrix metalloproteinases and, finally, it stimulates secretion of the acute phase proteins[82]. IL-6 is secreted directly into the portal circulation; thus, it reaches the liver where it stimulates release of CRP[11], an important predictor of future cardiovascular events both in patients with documented cardiovascular damage and in apparently healthy people[83].

VISFATIN

Visfatin, identified in 2004, derives its name from the fact that it is produced mainly in visceral fat. It is composed of 491 amino acids and has a molecular weight of 52 kDa. Visfatin gene corresponds to the gene of the Pre-B cell colony enhancing factor (PBEF). PBEF was described in 1994 as a cytokine produced by lymphocytes, involved in regulation of inflammatory mechanisms.

Interestingly, this adipokine is produced by macrophages resident in adipose tissue and not directly by adipocytes. In this regard, the levels of visfatin are believed to be the expression of macrophages infiltrating the adipose tissue, where they produce it in response to inflammatory signals[84]. Circulating levels of visfatin are closely correlated with white adipose tissue accumulation[9]. However, the relationship between circulating visfatin levels and anthropometric and metabolic parameters of obesity and type 2 diabetes is still not completely understood. The role of visfatin in cardiovascular disease is not clear. Increased expression of visfatin has been demonstrated in macrophages of human unstable carotid and coronary atherosclerotic plaques[85]. Again, endothelial dysfunction has been described in those patients with elevated plasma levels of visfatin[86]. Moreover, it has been observed that visfatin is able to increase the expression of adhesion molecules by activating the transcription factor NF-κB[87]. Taken together, these data suggest that visfatin might play a role in plaque destabilization.

"OTHER" ADIPOKINES

Several "other" adipokines with paracrine/endocrine activities are produced by adipose tissue. Some of these molecules have been partially characterized: apelin is a bioactive peptide produced by adipocytes, stromal vascular cells and cardiac myocytes. In obese patients with hyperinsulinemia, increased plasma levels of apelin are measurable[88]. In animal models of heart failure, cardiac apelin is down-regulated by angiotensin Ⅱ, while its production is restored after treatment with an angiotensin receptor 1 antagonist[89]. In rats, the cardiac production of apelin is increased by hypoxia[90] and ischemia[91]. In spontaneously hypertensive rats, exercise has also been shown to stimulate the production of apelin[92]. This molecule also has a positive hemodynamic effect, acting with an inotropic mechanism in rats with heart failure, as well as in isolated cardiomyocytes[93]. In humans, low plasma apelin was observed in patients with chronic heart failure[94] and in patients with atrial fibrillation[95]. In these, cardiac resynchronization therapy is accompanied by increases in

Table 1 Sources and potential role in cardiovascular disease of key adipokines

Adipokine	Primary source(s)	Potential role in CVD
Adiponectin	Adipocytes	↑ Insulin sensitivity, energy consumption, fatty acid oxidation ↓ Oxidative stress Anti-inflammatory activity ↓ TNF-α, IL-6, interferon-c ↑ IL-1R antagonist Modulation of chemokine expression Improved endothelial function eNOS induction ↑ NO ↓ ROS regulation of adhesion molecules Regulation of macrophage function Antiaggregants effects Decreased progression of atherosclerotic lesions
Leptin	Adipocytes	Appetite regulation and modulation of energy expenditure Independent prognostic marker of ACS Modulation of blood pressure Regulation of platelet aggregation and induction of arterial thrombosis TF, CRP and adhesion molecules induction in endothelial cells TF induction in peripheral blood mononuclear cells Maintenance of progression of atherosclerotic disease
Resistin/RELMs	RELM-α: Adipose tissue macrophages (human), adipocytes (mice) RELM-β: Tumor and gastro-intestinal cells RELM-γ: Hematopoietic tissue	Induction of insulin resistance Cell proliferation (RELM-β) Cytokine-like functionality (RELM-γ) Pro-inflammatory activity Independent predictive marker of atherosclerosis and severity of ischemic injury Effects on endothelial cells ↑ Adhesion molecules, cytokines, TF, plasminogen activator inhibitor, von Willebrand factor, endothelin ↓ e-NOS expression Smooth muscle cell proliferation and migration
TNF-α	Inflammatory cells, monocytes, macrophages, adipocytes	Reduction of insulin signaling Induction of insulin resistance Maintaining proinflammatory state and atherosclerosis
IL-6	Inflammatory cells, stromal vascular fraction cells, adipocytes, liver, muscle	Induction of insulin resistance Maintaining pro-inflammatory status Modulation of pro-inflammatory cytokines and pro-thrombotic mediators release Promotion of lipoproteins oxidation Activation of matrix metalloproteinase Induction of CRP production by the liver
Visfatin	Lymphocytes, macrophages, adipocytes, other cells	Monocyte chemotactic activity Endothelial dysfunction Atherosclerotic plaque destabilization TF induction
Other adipokines		
Apelin	Adipocytes, stromal vascular cells and cardiac myocytes	Cardiomyocyte function regulation
Omentin	Stromal vascular cells of visceral adipose tissue	↑ Insulin-stimulated glucose uptake in both Low levels in severe coronary atherosclerotic disease and arterial stiffness and carotid plaque in patients with diabetes Possible marker of metabolic dysfunction
Vaspin	Visceral and subcutaneous adipose tissue	Reduced plasma and mRNA levels in patients with unstable angina Low serum concentrations in patients with carotid atherosclerosis

ACS: Acute coronary syndrome; CRP: C-Reactive protein; eNOS: Endothelial nitric oxide synthase; IL: Interleukin; IL-1R: Interleukin-1 receptor; NO: Nitric oxide; RELM: Resistin like molecule; ROS: Reactive oxygen species; TF: Tissue factor; TNF: Tumor necrosis factor.

the concentrations of apelin[96]. Despite the available evidence, it is still unclear whether the form of metabolically active apelin is produced by adipose or by cardiac tissue. Thus, more studies are needed to clarify the role of this interesting peptide in the pathophysiology of cardiovascular disease and its potential therapeutic use.

Omentin is a secretory protein selectively expressed in the visceral adipose tissue, where it is synthesized by the visceral stromal vascular cells[97,98]. It has also been found in the human lung, intestine, ovaries, placenta and heart[98]. Omentin plasma levels are reduced in obese patients[99]. Conversely, elevated levels of omentin are measurable in the plasma of lean subjects with increased levels of adiponectin and high-density lipoproteins[99,100]. Omentin increases insulin-stimulated glucose uptake in both omental and subcutaneous adipocytes and promotes Akt/PKB phosphorylation[101]. Interestingly, it has been shown that low levels of omentin are measurable in patients with severe coronary atherosclerotic disease[102-104]. Finally, the association of circulating omentin level with arterial stiffness and carotid plaque in patients with diabetes has been demonstrated[105]. Recently, it has been proposed that omentin

might be an early marker of metabolic dysfunction[106].

Vaspin is a novel adipokine expressed in the visceral and subcutaneous adipose tissue, involved in the development of obesity and insulin resistance[107-110]. The relationship between vaspin and cardiovascular disease is still obscure. It has been demonstrated that patients with unstable angina have reduced plasma and mRNA levels of this adipokine[111]. In addition, vaspin serum concentrations were significantly low in patients with atherosclerosis of carotid arteries[112].

Table 1: Overview of adipocitokines and of their potential cardiovascular functions

CONCLUSION

It is well established that obesity and cardiovascular events are closely related. However, although it has been clearly demonstrated that obesity is also associated with other conditions that may accelerate atherosclerosis, the molecular mechanisms underlying these phenomena are not fully defined yet. In this context, adipose tissue, abundantly represented in obese individuals, might play a role by producing substances, called adipokines, with an active role in the pathophysiology of cardiovascular disease. Although some of these molecules, such as adiponectin, leptin and resistin, now have a well defined position in the complex network between inflammation, obesity and cardiovascular diseases, many others are still poorly defined functionally. It seems clear that the adipokines panorama needs new experimental evidence and clinical trials to compose the complex puzzle that link a "modern" and wellness disease like obesity with cardiovascular disease, the leading cause of mortality in industrialized world. As in a complex crime scene, we have several potentially guilty candidates.

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BHS/PCCS/Takeda Workshop for Nurses & Pharmacists
Bristol, United Kingdom

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BHS Hypertension & Cardiovascular Risk Spring Update for Nurses
Aberdeen Royal Infirmary,
Aberdeen, United Kingdom

February 10-12, 2012
Malaysian Society of Hypertension 9th Annual Scientific Meeting 2012
Kuala Lumpur, Malaysian

February 24, 2012
BHS Hypertension Masterclass
NICE Hypertension Guidelines: Essential Hypertension and Pregnancy
The Møller Centre, Churchill College,
Cambridge, United Kingdom

February 25- 28, 2012
Serbian Society of Hypertension 3rd International Meeting 2012
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March 3-5, 2012
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Cape Town, South Africa

March 14-18, 2012
9th Mediterranean Meeting on Hypertension and Atherosclerosis
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Excel Centre,
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2012 American Society of Hypertension Annual Scientific Meeting & Exposition
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The columns in the issues of *WJH* will include: (1) Editorial: To introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (6) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (7) Original Articles: To originally report the innovative and valuable findings in hypertension; (8) Brief Articles: To briefly report the novel and innovative findings in hypertension; (9) Case Report: To report a rare or typical case; (10) Letters to the Editor: To discuss and make reply to the contributions published in *WJH*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: To introduce and comment on quality monographs of hypertension; and (12) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in hypertension.

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Acknowledgments

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Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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Italics

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